In the matter of:
US 10/820 553

in the name of
Paedipharm Arzneimittel GmbH

I, Dr. Dietmar Forstmeyer, c/o BOETERS & LIECK, Oberanger 32, D-80331 München, Germany, do solemnly and sincerely declare as follows:

1. I am fully conversant with the English and German languages.

2. The attached is a translation which I have made in English of DE 198 16 143.3 in the name of Paedipharm Arzneimittel GmbH which I certify to be a true and correct translation into the English language to the best of my knowledge and belief.

AND I MAKE this solemn declaration, conscientiously believing the same to be true, this 28th day of August 2007.

(Dr. Dietmar Forstmeyer)

Your reference: 11372

Translation of DE 198 16 143.3

Paedipharm Arzneimittel GmbH

Transdermal delivery system (TDS) with electrode network

1. State of the Art

In the pharmaceutical industry's permanent search for optimisation of the administration of medicaments, transdermal delivery systems (TDSs) today occupy a significant position. In the areas of use realised so far (e.g. hormones, hypertension, pain, nicotine replacement), TDSs have already reached a worldwide turnover in excess of $ 2 billion. With all of the advantages of TDSs for patients and for the health cost system, the possibility of using such delivery systems is currently still restricted by permeability limits, which stem from the physico-chemical properties of the substances to be delivered. Many known active ingredients will be possible candidates for transdermal delivery as soon as a system is available that, for example, brings about permeability to larger molecules. The additional market potential is enormous. For some years there have therefore been technological attempts to improve the permeability to substances, for example the use of absorption enhancers in passive TDSs, or iontophoretic systems.

In order to transport a substance/active ingredient through the skin, customary TDSs make use of passive concentration-dependent diffusion along the concentration gradient between the TDS and the *stratum corneum* of the skin. Only very small molecules, however, can be forced through the skin using that mechanism. Larger, more complex molecules, such as insulin, LH-RH etc., require an additional driving force in order to pass through the skin into the bloodstream.

One method of applying an additional diffusion-increasing force is iontophoresis, that is to say the transport of molecules by means of an applied electrical field. For that purpose, a difference in electrical potential is generated between the substance/active ingredient carrier and the patient. The molecules, present in ionic form, are then driven from the conductive substance/active ingredient reservoir into the skin by means of electrostatic repulsion. The release of the substance/active ingredient over time can be accurately controlled by corresponding control of the driving electromotive force. This is a critical variable, especially in the case of an iontophoretic insulin system. Owing to the small therapeutic range of the active ingredient in that case, it is absolutely necessary that the permeation through the skin is controlled by the release from the system.

Supplied with iontophoretic systems are external control devices which are connected to the system by cable. Also known from the patent literature are arrangements that consist of integrated control units associated with a substance/active ingredient reservoir and electrodes (see below).

Iontophoretic transdermal therapeutic systems, as known, for example, from DE 3 703 321 C2, WO 92/04938, WO 87/04936, US 3 991 755, US 4 141 359 or WO 91/16077, generally consist of a combination of two electrodes, wherein one electrode or both electrodes is/are each connected to a substance/active ingredient reservoir. By means of a voltage applied to both electrodes it is then possible, once the iontophoretic system has been applied to the skin, for ionised substance/active ingredient molecules to be forced through the skin by means of electrostatic repulsion from the electrode that is charged in the same sense as the substance/active ingredient.

The basic construction of iontophoretic systems always comprises a cathode and an anode, which serve to generate a direct flow of current through the body. Accordingly, the geometric spacing between the electrodes must be such that there can be no short-circuiting at the skin surface. The electrodes in such arrangements are in direct contact with aqueous buffer solutions, which can be immobilised in gels. The electric contact with the skin is through those aqueous preparations. Ion-containing liquid therefrom is

able to spread along the surface of the skin and thus bring about a direct flow of current between the electrodes. Such a system therefore has to be of a certain minimum size in order to be able to give rise to insulation of the electrodes.

In order to avoid burns to the skin tissue, prevent polarisation of the electrodes and hydrolysis of tissue water (from approximately 1.7 V on), which can result in a painful shift in pH, iontophoretic systems are operated with a pulsed direct voltage or alternating voltage, the nature of the pulse (form, height, length) influencing the compatibility and effectiveness of the iontophoretic system. The field is generated over a wide area over the entire TDS and can be regulated only roughly, if at all. The entire system is therefore either active or switched off. Since the skin requires phases of recovery between voltage applications, for example in order for the reservoir built up during the iontophoresis to be emptied again, the result is that the release of active ingredient is not continuous and consequently also blood levels vary.

The current commercial forms of iontophoretic TDSs are very complex and expensive. The electrodes used are usually noble-metal-coated metal discs, the counterelectrodes are, for example, standard electrodes, all measures for avoiding the possible occurrence of polarisation. The electrode gels must, as stated hereinabove, be so arranged as to be isolated from each other and must not leak. All in all, the iontophoretic TDSs currently available are large, expensive and not very flexible with regard to the possibility of their being controlled. To harness the advantages of voltage-controlled substance/active ingredient permeation generally, however, requires simple and more flexible TDSs that are less expensive to produce.

Electroporation, which has been described recently and which operates with very brief (a few ms) and very high voltages (100-200 V), is not discussed herein.

2. Description of the invention

The problem underlying the invention is to make available an "intelligent" electrically controlled TDS that provides the properties described hereinabove.

The "network-array" TDS provided is a novel category of transdermal delivery systems. The network-array TDS consists chiefly of four components:

1) a carrier layer, on one side of which a substance/active ingredient matrix is applied and an electrode network is printed,

2) a rewritable microchip, for example securely bonded to the carrier layer,

3) a button battery or sheet battery, for example in a pocket in the carrier layer, as reusable energy source,

4) a reading and writing device for writing to the microchip.

2.1
The carrier layer

The size of the network-array TDS will not differ from the size of conventional passive TDSs (a few 10s of cm^2). The carrier layer is provided with a network of punctiform pairs of electrodes by printing (etching) on both sides, the geometry of the pairs of electrodes being such that a concentrated electric field is generated in the region of the two antipodes. The field geometry and the level of the applied potential difference is so chosen that the substance/active ingredient ions are driven from the substance/active ingredient matrix into the skin. Actuation of the individual electrodes is effected in a grid-like manner, systematically or by way of a random generator.

2.2 Microchip

Located at the edge of the carrier layer and bonded thereto is a microchip (optionally) having an electromagnetically rewritable memory. The chip controls the above-mentioned electrodes according to a prescription, it being possible for the individual parameters of a patient (optionally) to be taken into consideration in the course of therapy. For that purpose the patient or the attending doctor obtains a card-reading and -writing device. Before each treatment the patient's individual data are transferred by the reading device into the chip memory. In accordance with the data fed in, the patient then receives the active ingredients in an optimum dosage by way of the so-programmed TDS.

2.3 Energy source

One or more Li-button cells or corresponding sheet batteries are used for the energy source. For that purpose the carrier layer is provided, for example in direct proximity to the microchip, with a pocket having corresponding terminals into which the battery can be inserted. The capacity of such a cell is sufficient for one or more TDS deliveries, depending on the substance/active ingredient and the duration of use, so that the batteries can generally be used repeatedly.

2.4 Writing/reading device

The function of this has already been described above.

2.5 Differences from iontophoretic systems.

The electrode-network TDS consists of a plurality of pairs of electrodes which are printed on the upper side and underside of the carrier layer of the TDS (electrode network). With such an arrangement of electrodes, very economic large-scale manufacture of electrodes and TDSs is possible using standard printing methods. The printed layer does not lose its flexibility. The spacing of the counterelectrodes is determined very precisely by means of the thickness of the layer. The spacing of the

pairs of electrodes in the lateral direction can be varied very simply by means of the printing pattern. The spacing of the pairs of electrodes from one another is so arranged that separate actuation of the individual pairs is possible. The electrode area is typically from 0.1 to 10 cm^2.

The nature of the application of the electric field in the electrode-network TDS means that for the first time a variable change of state of any areas of the TDS is possible. Portions of the TDS can be positively charged, while at the same time other portions are negatively charged or uncharged. By means of the TDS a repeating pattern of the distribution of the electric field can be constructed, it being possible for the pattern to be of linear or two-dimensional design along the electrode networks or the electrodes or electrode pairs. It is thus possible to consider the field strength requirements of different substances/active ingredients individually, for example to activate partial areas of the TDS while other areas are at rest, so that the skin there can "recover". By choosing a suitable field strength, the depth of penetration of the field into the skin can be varied. When "empty", that is to say substance-/active ingredient-free, electrode-network systems are used, substances/active ingredients are able to migrate along the field lines of the directed field from the skin and into the reservoir, where they can be analysed for diagnostic purposes.

A fundamental difference from iontophoretic systems is that ionised molecules migrate along the field lines inside the substance/active ingredient reservoir. This can be carried out in media of low electrical conductivity or in electrically non-conductive media. It is thus possible to arrange oppositely-charged electrodes within one plane of the TDS without using a special insulator. When the chosen field strength of the electric field is so great that the field can penetrate into the skin with adequate intensity, the penetration of charged substance/active ingredient molecules into the skin is influenced, penetration enhancement generally being desired.

The electrode networks, electrodes or pairs of electrodes can be operated with constant or pulsed direct voltage or alternating voltage of varying wave forms.

Since the skin does not come into contact with the electrodes, the use of the electrode-network TDS cannot result in burns or in hydrolysis of tissue water. The compatibility of the systems according to the invention with the skin is accordingly distinctly improved compared with iontophoretic systems.

As carrier layers there may be used polyester, polyethylene or polypropylene layers of thicknesses of from 10 to 1000 μm.

The electrodes may be of copper, silver, gold, platinum or other conductive materials, which are applied to the carrier layer by means of appropriate printing methods, such as relief printing, screen printing or etching etc..

The substance/active ingredient reservoir may be a substance-/active ingredient-containing pressure-sensitive contact adhesive, a substance-/active ingredient-containing gel or an immobilised substance/active ingredient solution, the pH value of which enables ionisation of the substance or active ingredient in question.

The substances/active ingredients used may be substances/active ingredients from the class of the opioids, anti-asthmatics, regulatory peptides, parasympathomimetics, parsympatholytics or local anaesthetics, without being limited thereto. The concentrations of the substances/active ingredients in the reservoirs can vary widely, and they depend to a varying extent on the desired rate of release and the required permeation through the skin. Typical concentrations lie in the range from 0.1 to 10 % of the total mass of the reservoir. The permeation of the skin by the substances/active ingredients in question can be further influenced by admixing conventional permeation enhancers.

Patent Claims

1. Transdermal delivery system (TDS) having

- a carrier layer on one side of which a substance/active ingredient matrix is applied and an electrode network is printed,
- a possibly rewritable microchip, securely bonded to the carrier layer,
- a possibly reusable battery,
- a reading and writing device for writing to the microchip.

2. Delivery system according to claim 1, characterised by a carrier layer having a thickness in the range from 10 to 1000 μm.

3. Delivery system according to claim 1 or 2, characterised in that the substance/active ingredient reservoir is formed by a contact adhesive, a gel or an immobilised solution for the substance/the active ingredient.

4. Delivery system according to any one of the preceding claims, characterised in that the carrier layer carries a network of pairs of electrodes, the electrodes of each pair arranged at opposite sides of the carrier layer.

5. Delivery system according to any one of the preceding claims, characterised in that the electrode network has been applied by printing.

6. Delivery system according to any one of the preceding claims, characterised in that, each pair of electrodes is actuatable individually.

7. Delivery system according to any one of the preceding claims, characterised in that, each pair of electrodes is actuatable in groups.

8. Delivery system according to any one of the preceding claims, characterised in that electrodes chargeable in the same or in opposite senses are arranged on each of the two sides of the delivery system.

9. Delivery system according to any one of the preceding claims, characterised in that the microchip is securely bonded to the carrier layer.

10. Delivery system according to any one of the preceding claims, characterised in that the microchip is a chip that is programmable according to a prescription.

11. Delivery system according to any one of the preceding claims, characterised in that the battery is a button battery or sheet battery.

12. Delivery system according to any one of the preceding claims, characterised in that the battery is provided in a pocket in the carrier layer.

Abstract

The problem underlying the invention is to make available an "intelligent" electrically controlled TDS that provides the properties described hereinabove.
The "network-array" TDS provided is a novel category of transdermal delivery systems.
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